Oral Apremilast for the Treatment of Plaque Psoriasis

James Q. Del Rosso, DO; Leon Kircik, MD

(*J Clin Aesthet Dermatol.* 2016;9(9):43–48.)

Abstract

This article provides an update on the use of oral apremilast, a phosphodiesterase-4 (PDE4) inhibitor, for the treatment of plaque psoriasis. Emphasis is placed on safety evaluations, although efficacy considerations are also addressed. Both two-year and three-year data analyses support the favorable safety profile reported in pivotal trials with this agent. Although effective in many study subjects despite baseline characteristics, higher response rates were noted in those with a baseline psoriasis area and severity index (PASI) score <20 and in subjects not previously treated with systemic therapy for psoriasis. Gastrointestinal (GI) side effects are the most common adverse events (AEs) reported, especially during the first few weeks of use; recommendations on management of GI AEs are discussed. Psychological AEs appear to be rare, including with prolonged durations of use, and are not clearly associated with the drug itself as depression and suicidal behaviors are common in individuals with psoriasis. Data reported through up to 182 weeks of exposure to apremilast do not support an association with cardiac AEs, emergence of malignancies, enhanced predilection to develop significant opportunistic infections, or reactivation of occult infection, such as tuberculosis.

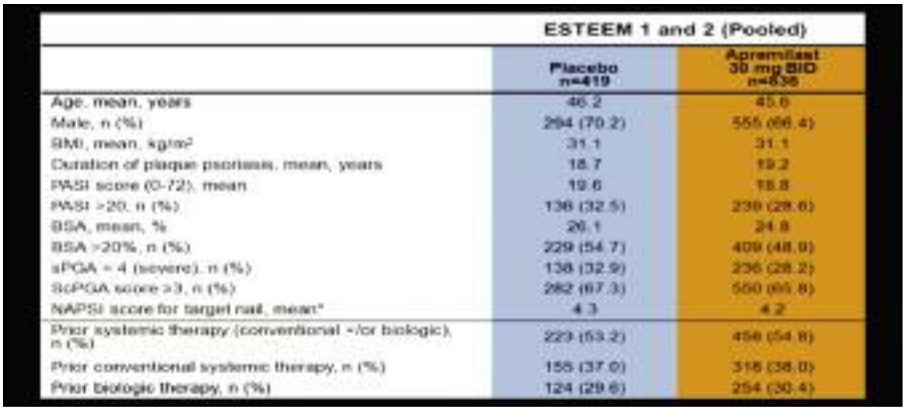
Introduction

Apremilast is an inhibitor of phosphodiesterase-4 (PDE4) that is available as an oral tablet formulation approved by the United States Food and Drug Administration (FDA) for the treatment of patients with moderate and severe plaque psoriasis (PlqPso), for those with PlqPso who are candidates for systemic therapy or phototherapy, and for active psoriatic arthritis (PsA) in adults.[1–3] The efficacy and safety of apremilast in subjects with PlqPso has been reviewed in detail elsewhere and demonstrates that although usually with a slower onset than biologic agents, some patients may achieve satisfactory control provided they allow for an adequate trial of therapy.[1–3] The results of randomized, controlled pivotal trials (RCTs) with this agent are summarized in the next section. In addition to apremilast showing efficacy in PlqPso of the trunk and extremities, it has also shown efficacy for nail psoriasis and moderate-to-severe scalp psoriasis, and has demonstrated marked and rapid reduction in pruritus associated with PlqPso.[2–8] The authors have also observed effectiveness of apremilast for psoriasis involving the male genitalia. The mode of action of apremilast in PlqPso appears to relate to modulation of inflammation via intracellular inhibition of PDE4; the resultant increase in levels of cyclic adenosine monophosphate (cAMP) and reduction in AMP diminishes cellular inflammation and keratinocyte activation/proliferation.[1–3,9–11]

Overall, apremilast demonstrates a favorable safety profile based on data accumulated from studies of adult subjects treated with PlqPso and PsA.[1–4,8,11–13] Gastrointestinal (GI) side effects (e.g., nausea, changes in bowel movement quality and/or frequency) have been reported to be the most common adverse reactions associated with apremilast use.[1–3] The drug appears to exhibit negligible immunosuppressive activity, with no specific recommendations for pre-treatment laboratory testing or exclusion of underlying infections such as tuberculosis.[1–4,11,14] This article reviews more recent information on apremilast for treatment of PlqPso with emphasis on both short-term and long-term study outcomes and other clinically relevant data from clinical trials.

Overview from Pivotal Studies at 16 Weeks, 104 Weeks, and 182 Weeks, with Emphasis on Safety Data

The Phase 3 pivotal trials (ESTEEM 1 and ESTEEM 2) demonstrated favorable efficacy and safety of apremilast 30mg twice daily (BID) as compared to placebo with primary endpoint analyses at Week 16 showing statistical superiority as discussed above. Both trials encompassed 836 subjects in the active study drug (apremilast) arms and 419 subjects in the placebo arms, with a mean age of 45.6 to 46.2 years and mean disease duration of 18.7 to 19.2 years; 48.9 to 54.7 percent of enrolled subjects presented with a body surface area (BSA) >20 percent



	ESTEEM 1 and 2 (Pooled)	
	Placebo n=419	Apremilast 30 mg BID n=836
Age, mean, years	46.2	45.6
Male, n (%)	294 (70.2)	555 (66.4)
BMI, mean, kg/m²	31.1	31.1
Duration of plaque psoriasis, mean, years	18.7	19.2
PASI score (0-72), mean	19.6	18.8
PASI >20, n (%)	136 (32.5)	239 (28.6)
BSA, mean, %	26.1	24.8
BSA >20%, n (%)	229 (54.7)	409 (48.9)
sPGA = 4 (severe), n (%)	138 (32.9)	236 (28.2)
ScPGA score >3, n (%)	282 (67.3)	560 (66.8)
NAPSI score for target nail, mean*	4.3	4.2
Prior systemic therapy (conventional +/or biologic), n (%)	229 (53.2)	456 (54.8)
Prior conventional systemic therapy, n (%)	155 (37.0)	316 (38.0)
Prior biologic therapy, n (%)	124 (29.6)	254 (30.4)

Figure 1. Oral apremilast 30mg twice daily for plaque psoriasis (subgroup characteristics from pivotal studies [pooled data, ESTEEM 1 and ESTEEM 2]).[14]
BMI=Body Mass Index; PASI=Psoriasis Area and Severity Index; BSA=Body Surface Area; sPGA=Static Physician Global Assessment; ScPGA=Scalp Physician Global Assessment; NAPSI=Nail Psoriasis Severity Index

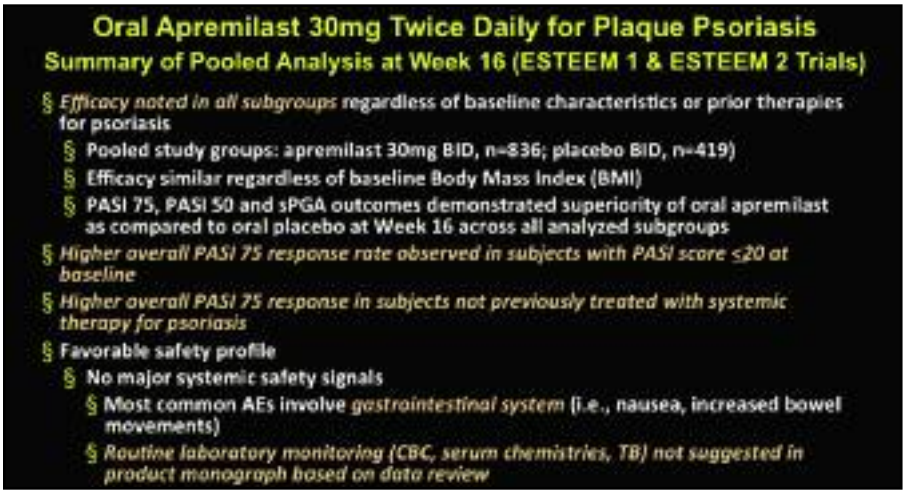


Figure 2. Oral apremilast 30mg twice daily for plaque psoriasis (summary of pooled analysis at Week 16 [ESTEEM 1 & ESTEEM 2 trials]).[1,2,14]
BID=twice daily; PASI=Psoriasis Area and Severity Index; sPGA=Static Physician Global Assessment; AEs=adverse events; CBC=complete blood cell count; TB=tuberculosis

and 28.2 to 32.9 percent with severe disease based on the Static Physician Global Assessment (sPGA) grading scale defined in the FDA-approved study protocol.[1,2] A summary analysis of baseline study characteristics and subgroups from ESTEEM 1 and ESTEEM 2 trials is shown in Figure 1.

Efficacy. In the two Phase 3 RCTs, enrolled subjects ≥18 years of age were affected by PlqPso with body surface area (BSA) involvement >10 percent, an sPGA rating of moderate (grade 3) or severe (grade 4), and a Psoriasis Area and Severity Index (PASI) score >12. In ESTEEM-1, 33.1 and 5.3 percent achieved PASI 75 at Week 16 in the apremilast group (n=562) and in the placebo group (n=282), respectively (P<0.0001).[1,2] The percent of subjects achieving PASI 50 at Week 16 was 58.7 and 17.0 percent in the apremilast group and placebo group, respectively.[1,2] In ESTEEM-2, 28.8 and 5.8 percent achieved PASI 75 at Week 16 in the apremilast group (n=274) and in the placebo group (n=137), respectively (P<0.0001).[1] The percent of subjects achieving PASI 50 at Week 16 was 55.5 and 19.7 percent in the apremilast group and placebo group, respectively.[1] Specific outcomes, such as PASI 75, PASI 50, and sPGA demonstrated superiority with apremilast as compared to placebo across all analyzed subgroups; at Week 16, higher overall PASI 75 response rates were observed in subjects with PASI score <20 at baseline and in subjects not previously treated with systemic therapy for psoriasis (Figure 2).[14] A comparative summary of study outcomes in apremilast-treated and placebo-treated subjects through 104 weeks in the ESTEEM-1 RCT is outlined in Figure 3.

Author commentary on efficacy. Oral apremilast is a viable option for the treatment of PlqPso in subjects who are not adequately controlled by topical therapy; in those with extent of involvement that makes topical therapy too cumbersome, inconvenient, and/or messy; and in those who are not candidates for or are not willing to undergo biologic therapy. This agent appears to be especially useful in patients with BSA <20 percent and in those with scalp involvement. An adequate trial of at least 8 to 12 weeks is suggested as the onset of appreciable clinical efficacy may be slow in some individuals.

Safety. The design of both Phase 3 RCTs with apremilast for PlqPso provided for treatment extensions based on specific criteria which allows for additional data over longer durations of treatment.[2,3,14] The

following reviews data on specific adverse events (AEs) reported during clinical trials, with an attempt to put into perspective the potential magnitude of their clinical relevance and how clinicians may best monitor their patients.

Gastrointestinal side effects. Based on studies with apremilast for both PlqPso and PsA, GI side effects are the most common AEs reported.[1–3,15,16] Pooled analysis was completed evaluating GI side effects in the RCTs for PlqPso (ESTEEM 1 and 2) and in the RCTs for PsA (PALACE 1, 2, and 3).[17] Outcomes after 16 weeks noted diarrhea in 17.8 percent (148/832 ESTEEM trials) and 16.5 percent (82/497 PALACE trials) treated with apremilast 30mg BID compared to 6.7 percent (28/418 ESTEEM trials) and 2.8 percent (14/495 PALACE) in placebo-treated subjects. Nausea was reported in 16.6 percent (138/832, ESTEEM trials) and 15.1 percent (75/497, PALACE trials) with apremilast 30mg BID and 6.7 percent (28/418, ESTEEM trials) and 4.4 percent (22/495, PALACE trials) in the placebo BID study arms. The majority of subjects reported these GI side effects within the first few weeks of starting therapy, with a tendency for resolution with continued use of study drug; incidences of diarrhea and nausea decreased with increasing exposure times to therapy over 52 weeks of study observation, with median duration of diarrhea and nausea episodes reported to be 16 days.[17] No differences were noted among the PlqPso and PsA subgroups regarding GI AEs.[17]

It is important to recognize that during the PlqPso and PsA RCTs (ESTEEM, PALACE), protocol definitions for reporting of patient-specific details related to diarrhea or nausea were not well-described; bowel movement (BM) frequency and specific stool characteristics using scales recognized in GI literature were not assessed in these trials. Both diarrhea and nausea were documented based on patient reporting of their occurrence and severity ratings completed by subjects and investigators. Accurate reporting of nausea seems more intuitive due to anticipated familiarity with this subjective symptom at some point in a subject's life experience. However, reporting of diarrhea included change in frequency of BMs (such as twice versus once a day) and/or change in quality of BMs (i.e., looser stools than usual), and do not necessarily reflect an immediate need for defecation, such as with more explosive or urgent diarrhea. Such distinctions are of importance to clinicians when educating or managing patients, and unfortunately could not be gleaned from the data capture in the pivotal RCTs with apremilast for both PlqPso and PsA. Also, no specific instructions were given for the management of diarrhea or nausea; these events were managed at the discretion of the investigators. Many subjects continued therapy with resolution of these side effects, with some using oral antidiarrheal agents such as loperamide (Imodium).

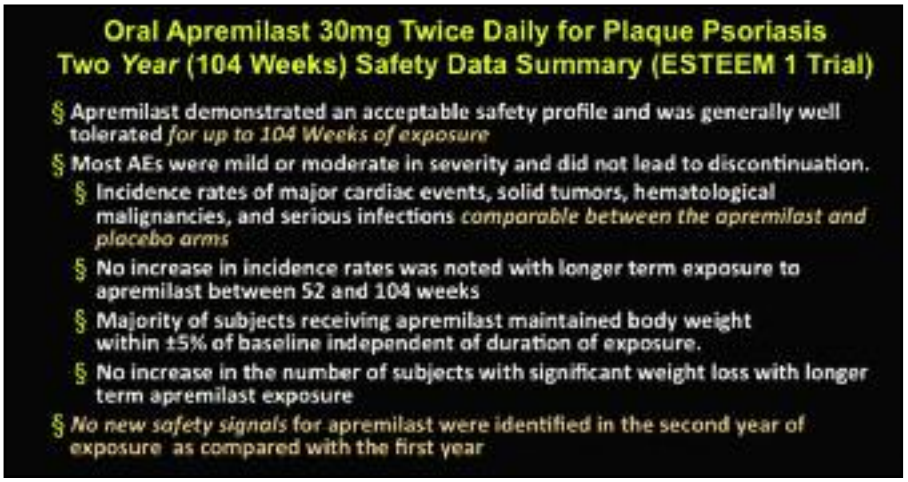


Figure 3. Oral apremilast 30mg twice daily for plaque psoriasis (two year [104 Weeks] safety data summary [ESTEEM 1 Trial][14,15]
AEs=adverse events

The long-term safety of apremilast 30mg BID was analyzed in the pooled population of subjects treated for PlqPso for <182 weeks in two RCTs (ESTEEM 1, ESTEEM 2).[18] The apremilast-exposure periods of 0 to ≤52 weeks and 0 to ≤182 weeks included all patients who received the drug regardless of when exposure to apremilast started. This analysis allows for differentiating the timing of AEs over the course of apremilast use for PlqPso. AE outcomes leading to discontinuation of drug in at least two subjects were reported with correlation to time period of exposure, defined as 0 to <52 weeks (n=1,184) and 0 to <182 weeks (n=1,184).

The number and percentage of subjects during 0 to <52 weeks and 0 to <182 weeks were 17 (1.4%) and 17 (1.4%), 11 (0.9%) and 12 (1%), 5 (0.4%) and 6 (0.5%), 3 (0.3%) and 3 (0.3%), 3 (0.3%) and 3 (0.3%), for nausea, diarrhea, vomiting, dyspepsia, and abdominal discomfort, respectively, supporting that the

TABLE 1. Management approaches for nausea and diarrhea

APPROACHES SUGGESTED FOR THE MANAGEMENT OF NAUSEA INCLUDE:[17]
Ingesting apremilast with food
Eating smaller more frequent meals
Avoiding excessive liquid intake with meals
Using anti-nausea medications, such as diphenhydramine (Benadryl: OTC), promethazine (Phenergan; Rx), or prochlorperazine (Compazine; Rx)
APPROACHES SUGGESTED FOR THE MANAGEMENT OF DIARRHEA INCLUDE:[17]
Ingesting apremilast with food
Maintaining adequate hydration (without large volume ingestion with food)
Eating smaller more frequent meals
Limiting caffeine, dairy, and artificial sweetener intake
Using anti-diarrheal medications, such as loperamide (Imodium: OTC), fiber-bulk forming agents (OTC), Bismuth subsalicylate (Pepto-Bismol, Kaopectate; OTC)

occurrence of GI AEs does not increase with more prolonged exposure to apremilast.[18]

Author commentary on GI side effects. The GI side effects of phosphodiesterase inhibition are believed to be due to increased cAMP in the GI mucosa, resulting in a secretory diarrhea pattern in some patients.[19] This is important as it supports that GI side effects associated with PDE4 inhibition have not been related to induction of inflammatory GI disease. To add, xanthines (i.e., caffeine) found in coffee, tea, and some soft drinks can increase cAMP through phosphodiesterase inhibition.[20] As a result, the authors empirically suggest to patients who heavily ingest these beverages to reduce their intake during the first few weeks of using apremilast and build up their intake slowly in an attempt to reduce the potential for early GI side effects (Table 1).

Depression. In clinical trials completed with apremilast versus placebo during phases of drug development, depression was reported in 1.3 percent (12/920) of apremilast-treated subjects and 0.4 percent (2/506) of placebo-treated subjects.[1–3,15]

One subject exposed to apremilast during clinical studies (0.1%, 1/1308) experienced depression rated as severe with treatment discontinued.[1,15]

Suicidal behavior was observed in 0.2 percent (1/506) of subjects treated with placebo and in 0.1 percent (1/1308) treated with apremilast, with one successful suicide occurring in the placebo study groups and one attempted (but not successful) suicide noted in the apremilast study groups.[1,15]

An analysis comparing the time periods of 0 to <52 weeks and 0 to <182 weeks included evaluation of reported rates for depression and suicidal ideation.

The number and percentage of subjects during 0 to <52 weeks and 0 to <182 weeks were 24 (2.0%) and 33 (2.8%), 1.0 (0.1%) and 2 (0.2%), 1.0 (0.1%) and 1.0 (0.1%), and 0 (0%) and 0 (0%) for depression, serious depression, suicide attempt, and completed suicide, respectively. These results show that the incidence of these psychological AEs do not appear to change appreciably with more prolonged exposure to apremilast; notably, subjects with a history of depression were not excluded from the Phase 3 pivotal studies.[18]

Author commentary on psychological side effects. Evaluation of a potential association between a given therapeutic agent and AEs of depression and suicidal ideation is confounded by the common occurrence of both depression and

thoughts of suicide in people with PlqPso.[21,22] In one study, approximately 10 percent of patients with PlqPso (N=607) were affected by major depressive disorder (MDD), with 35 percent of these patients reporting suicidal ideation. Risk factors for MDD in this population included severe PlqPso, female gender, PsA, and prior history of depression/anxiety.[21] It is prudent for clinicians to observe patients with PlqPso for signs of mood alteration or depression during office visits and inquire about the patient's frame of mind and potential psychological concerns. Depression and anxiety disorders are commonly present in patients with PlqPso, and suicidal ideation is not infrequent in those affected by depression.[21,22] These adverse psychological effects may occur in patients who are not on treatment or in those utilizing therapies for PlqPso, including biologic agents.[21] Although it is always possible that psychological disorders may be AEs associated with a given therapy, these events seem to be both rare and idiosyncratic, and may still be disease-associated or an individual predisposition as opposed to drug-associated.

Other potential adverse sequelae. In the analysis that was carried out for up to 182 weeks, rates of major cardiac events and malignancies were very low and comparable over both 0 to <52 weeks and 0 to <182 weeks in subjects treated with apremilast; there was no definitive evidence of direct causation by apremilast.[18] As the mean age of enrolled study subjects was approximately 50 years of age (range 40–60 years), malignancies of various types, especially skin, breast, and prostate, are expected to emerge consistent with the rate expected in the general population. The most common cancers identified over three years duration of observation in subjects exposed to apremilast during part or all of this time period (n=1,184) were nonmelanoma skin cancer (20 [1.6%]), breast cancer (3 [0.3%]), and renal cell carcinoma (2) [0.2%]); one case of prostate cancer and one case of hematologic malignancy (diffuse large B-cell lymphoma) were noted. As the mean age of enrolled study subjects was approximately 50 years of age (range average 41–61 years), malignancies of various types, especially skin, breast, and prostate, are expected to emerge consistent with what would be expected in the general population. The very low levels of malignancies and the diversity of cancer types reported suggests that the risk of malignancy induced by apremilast appears to be negligible. Serious opportunistic infections were not reported in subjects treated with apremilast. A summary of outcomes from the analysis completed on subjects treated with apremilast for up to 182 weeks are outlined in Figure 4.

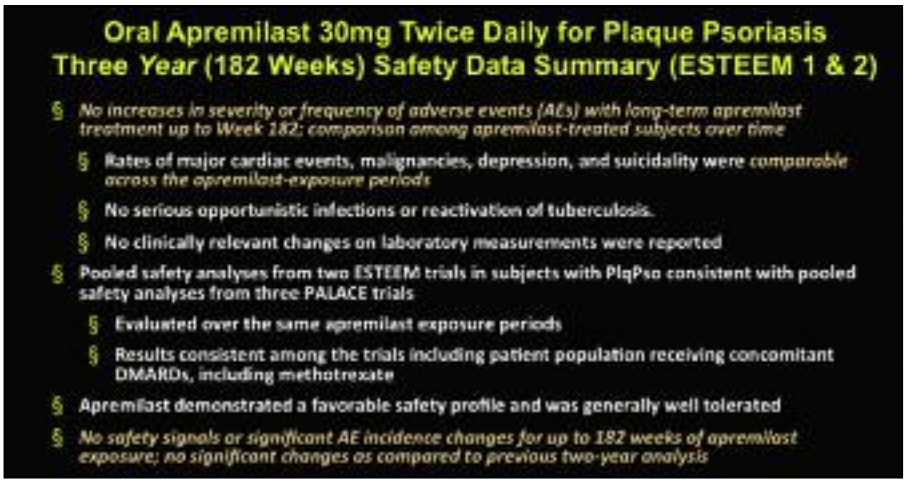


Figure 4. Oral apremilast 30mg twice daily for plaque psoriasis (three year [182 weeks] safety data summary [ESTEEM 1 & 2])[18]
DMARDs=disease-modifying antirheumatic drugs

Author commentary on other potential adverse sequelae. Data to date followed out through <182 weeks of exposure to apremilast do not support an association with cardiac AEs, emergence of malignancies (especially a given type of cancer), enhanced predilection to develop significant opportunistic infections, or reactivation of occult infection (i.e., tuberculosis). Although, apremilast does modulate inflammatory and immunologic cascades through PDE4 inhibition, this mode of action does not appear to cause immunosuppression associated with increased potential for opportunistic infections or malignancies. Continued pharmacovigilance is always prudent in order to detect and disseminate any new clinically relevant information to clinicians.

References

1. Otelza [package insert]. Summit, NJ: Celgene Corporation; 2014.
2. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled

trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol.* 2015;73(1):37–49.
3. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks, a phase III randomized controlled trial (ESTEEM 2). *Br J Dermatol.* 2015;173(6):1387–1399.
4. Gisondi P, Girolomoni G. Apremilast in the therapy of moderate-to-severe chronic plaque psoriasis. *Drug Des Devel Ther*. 2016;10:1763–1770.
5. Pasch MC. Nail psoriasis: a review of treatment options. *Drugs.* 2016;76(6):675–705.
6. Nguyen CM, Leon A, Danesh M, et al. Improvement of nail and scalp psoriasis using apremilast in patients with chronic psoriasis: phase 2b and 3, 52-week randomized, placebo-controlled trial results. *J Drugs Dermatol.* 2016;15(3):272–276.
7. Sobell JM, Foley P, Toth D, et al. Effects of apremilast on pruritus and skin discomfort/pain correlate with improvements in quality of life in patients with moderate to severe plaque psoriasis. *Acta Derm Venereol.* 2016;96(4):514–520.
8. Strand V, Fiorentino D, Hu C, et al. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. *Health Qual Life Outcomes*. 2013 May 10;11:82. doi: 10.1186/1477-7525-11-82.
9. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol.* 2012;83(12):1583–1590.
10. Schett G, Sloan VS, Stevens RM, et al. Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases. *Ther Adv Musculoskelet Dis.* 2010;2(5):271–278.
11. Chimenti MS, Gramiccia T, Saraceno R, et al. Apremilast for the treatment of psoriasis. *Expert Opin Pharmacother.* 2015;16(13):2083–2094.
12. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomized controlled trial. *Lancet.* 2012;380(9843):738–746.
13. Qu X, Zhang S, Tao L, et al. A meta-analysis of apremilast on psoriatic arthritis long-term assessment of clinical efficacy (PALACE). *Expert Rev Clin Pharmacol.* 2016;9(6):799–805.
14. Korman N, et al. Apremilast, an oral phosphodiesterase-4 inhibitor, in patients with moderate to severe plaque psoriasis: pooled 16-week efficacy in patient subgroups (ESTEEM 1 and 2). Poster presented at the 73rd annual meeting of the American Academy of Dermatology; San Francico, California; March 20–24, 2015.
15. Data on File, Apremilast (Otezla), Celgene Corporation, Summit, New Jersey.
16. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis.* 2014;73(6):1020–1026.
17. Abraham BP, Shah K, MD; Levi E, Sellin J. Apremilast for the treatment of psoriasis and psoriatic arthritis: management of gastrointestinal adverse effects. Poster presented at the 74th Annual Meeting of the American Academy of Dermatology, Washington DC; March 4–8, 2016.
18. Papp K, Sobell JM, Shah K, et al. Safety and tolerability of apremilast up to 182 weeks: pooled analyses from phase 3 clinical trials. Poster presented at the 74th Annual Meeting of the American Academy of Dermatology, Washington DC, March 4–8, 2016.
19. Lambert JA, Raju SV, Tang LP, et al. Cystic fibrosis transmembrane conductance regulator activation by roflumilast contributes to therapeutic benefit in chronic bronchitis. *Am J Respir Cell Mol Biol.* 2014;50(3):549–558.
20. Francis SH, Sekhar KR, Ke H, Corbin JD. Inhibition of cyclic nucleotide phosphodiesterases by methylxanthines and related compounds. *Handb Exp Pharmacol.* 2011;(200):93–133.
21. Lamb RC, Matcham F, Turner M, et al. Screening for anxiety and depression in people with psoriasis: a cross sectional study in a tertiary referral setting. *Br J Dermatol.* 2016 Jul 1. [Epub ahead of print].
22. Lakshmy S, Balasundaram S, Sarkar S, et al. A cross-sectional study of prevalence and implications of depression and anxiety in psoriasis. *Indian J Psychol Med.* 2015;37(4):434–440.

Dr. Del Rosso is Adjunct Clinical Professor (Dermatology), Touro University Nevada, Henderson, Nevada; Lakes Dermatology and Del Rosso Dermatology Research, Las Vegas, Nevada. Dr. Kircik is Clinical Associate Professor of Dermatology, Indiana University School of Medicine, Indianapolis, Indiana, Mount Sinai Medical Center, New York, New York; Medical Director, Physicians Skin Care, PLLC Louisville, Kentucky, DermResearch, PLLC, Louisville, Kentucky. Disclosures (related to this manuscript): Dr. Del Rosso is a speaker, consultant, and/or researcher for Anacor, Aqua, Allergan, Bayer, Celgene, Galderma, LeoPharma, Novartis, Pharmaderm, Promius, SunPharma, and Valeant. Dr. Kircik is either a speaker, consultant, or investigator for Amgen, Anacor, Aqua, Allergan, Bayer, Celgene, Coherus, Eli Lilly, Galderma, LeoPharma, Merck, Novartis, PharmaDerm, Promius, SunPharma, and Valeant. Address correspondence to: James Q. Del Rosso; E-mail: jqdelrosso@yahoo.com.

IN FOCUS